MEDICINE CABINET

Use of methadone

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Opiate dependence is a major public health problem associated with the transmission of deadly diseases (human immunodeficiency virus [HIV], hepatitis), criminal activity, accidental overdose, hospital admissions, and death. The treatment of opiate dependence is controversial, and in most patients, a lifelong duration is probably required.[1] Methadone is a synthetic opiate primarily used in the detoxification and maintenance of patients who are dependent on opiates—particularly heroin—and the treatment of patients with chronic, severe pain.

In the United States, methadone may be prescribed by physicians and dispensed by community pharmacies for analgesia as a Schedule II drug under the regulations of the Controlled Substances Act. However, when used for the treatment of opiate dependence, methadone's accessibility is restricted to practitioners, clinics, and pharmacies licensed by the Food and Drug Administration for this purpose.

PHARMACOLOGY AND MECHANISM OF ACTION

Methadone is a synthetic, long-acting opioid with pharmacologic actions qualitatively similar to morphine and is active by oral and parenteral routes of administration.[2] It is primarily a μ-receptor agonist and may mimic endogenous opioids, enkephalins, and endorphins and affect the release of other neurotransmitters—acetylcholine, norepinephrine, substance P, and dopamine.[3] This accounts for its analgesic and antitussive properties, respiratory depression, sedation, decrease in bowel motility, increase in biliary tone, hormone regulation and increase of prolactin and growth hormone release, miotic pupils, nausea, and hypotension. Patients develop tolerance and physical dependence following repeated use. The tolerance may be only partial for most of the pharmacologic effects. An abstinence syndrome consisting of lacrimation, rhinorrhea, sneezing, gooseflesh, nausea, vomiting, fever, chills, tremor, and tachycardia occurs on abrupt discontinuation of the opiate or the administration of an antagonist such as naloxone hydrochloride. There is cross-tolerance and cross-dependence among the various opiates. This is the premise for using methadone in the detoxification and maintenance of heroin people addicted to heroin. Due to the long half-life and duration of action of methadone, the abstinence syndrome is delayed and prolonged but less severe than that from a shorter-acting opiate such as heroin.

INDICATIONS AND DOSING

Maintenance

Maintenance therapy is the long-term administration of methadone hydrochloride to patients who are dependent on opiates. The aim is to substitute methadone, a legal, oral opiate with a long half-life, for the illicit, parenterally administered heroin, which is associated with a high risk of morbidity and mortality. Methadone maintenance therapy offers a reprieve from the daily life associated with the procurement and use of heroin and allows a person to reintegrate as a functional member of society. Methadone therapy achieves this by preventing opiate withdrawal symptoms, blocking the euphoric effects of heroin, and minimizing the craving for heroin. Methadone maintenance has been shown to reduce illicit heroin use,[4] decrease the incidence of infectious disease (such as HIV and hepatitis) commonly contracted through needle sharing,[5] reduce criminal activity,[6] improve social outcome,[7] and reduce mortality.[8]

A dose of 5 mg of parenteral heroin is approximately equivalent to 20 mg of oral methadone.[9] Because the purity of street heroin varies considerably, however, empiric methadone dosing is recommended instead of equivalent dosing based on recent heroin use.

The dosage of methadone in maintenance therapy remains controversial. It is usually started at 10 to 20 mg and increased in 10-mg increments until the withdrawal symptoms are controlled. Most patients can be maintained at 40 mg a day to control withdrawal symptoms but not eliminate drug craving. Evidence supports the need to administer higher doses of methadone for effectiveness.[10] In the past, it was common to administer the lowest dose possible to curb opiate withdrawal symptoms. However, because a major concern is the high risk of HIV conversion among persons using the intravenous drug–using population, methadone's effectiveness is more accurately measured by the incidence of illicit intravenous heroin use. Strain and coworkers showed that patients given methadone doses of 80 to 100 mg a day versus 40 to 50 mg a day had a much lower incidence of surreptitious, illicit heroin use during maintenance therapy.[10] In a retrospective study, Caplehorn and associates determined that patients receiving 40 mg of methadone a day were 2.2 times more likely to use heroin than patients receiving 80 mg a day when enrolled in a methadone maintenance treatment program.[11]

Detoxification

Methadone detoxification involves the short-term administration of methadone hydrochloride to blunt the abstinence symptoms of patients who are dependent on opiates and then tapering the dose of methadone with the goal of achieving a drug-free state. The major disadvantage of

Waiting in line for methadone at San Francisco General Hospital

detoxification in these patients is the high recidivism rate of heroin misuse after completing detoxification.[12] The high recidivism rate may be attributed to a physiologic state and abstinence syndrome that persists long after long-term opiate use ceases.[13]

For detoxification, treatment doses are usually started at 10 to 20 mg and increased in 10-mg increments until the withdrawal symptoms are controlled. A dosage of 40 mg a day controls the withdrawal symptoms for most patients but does not eliminate heroin craving. Once the dose required is established to eliminate withdrawal symptoms, the patient is stabilized on this dose for 2 to 3 days. Then the dose is reduced daily or every other day.[14] A 10% to 20% dose reduction is usually tolerated, but this must be tailored for each patient. If patients are experiencing abstinence symptoms or have a high risk of relapsing into heroin misuse, the practitioner should consider increasing the dose and slowing the tapering schedule. Individual tapering schedules may vary from weeks to months.[9] Patients should be monitored for withdrawal symptoms after the discontinuation of methadone, bearing in mind that withdrawal symptoms may not be evident for 48 to 72 hours following their previous dose.

Pain

Methadone is a good therapeutic alternative to morphine sulfate and other opiate analgesics in the treatment of severe, chronic pain.[15] It is well absorbed orally, has analgesic effects comparable to other μ-opiate receptor analgesics like morphine,[16] has a long half-life, and is not metabolized to any active metabolites that may pose a risk to the patient.

Morphine and methadone are both effective analgesic agents. In patients treated with opiates for chronic pain, the equivalent analgesic doses for morphine and methadone do not always follow a linear relation, so caution should be taken when switching a patient from morphine to methadone.[17]

Parenteral methadone is about twice as potent as oral methadone. The normal adult dosage of methadone is 2.5 to 10 mg every 3 to 4 hours as needed for severe pain and 5 to 20 mg every 6 to 8 hours as needed for severe, chronic pain (for example, for patients who are terminally ill).[9] The dosage and dosing interval of methadone for pain relief vary considerably. The dose should be adjusted to the individual needs of the patient.

Although methadone has a long half-life, analgesia is not related to the serum half-life, and frequent daily dosing intervals are usually required for pain relief.[18] Caution should be taken not to increase the dose too high or too frequently when initiating therapy because toxic effects may ensue. Adjunctive analgesics should be considered during the first few days of the initiation of the methadone regimen.

Methadone is a good alternative for patients who are being given maximum doses of morphine. However, determining the proper methadone dose based on a patient's current morphine requirement may be challenging. The relative equivalent analgesic dose of morphine to methadone has varied from 1:1 to 14:1 (14 mg of morphine to 1 mg of methadone).[17]

USE IN PREGNANCY

Methadone crosses the placenta and can cause fetal dependence.[19] Therefore, the administration of methadone during pregnancy should be limited to patients with an established opiate dependence. Opiate detoxification during pregnancy is not recommended because fetal distress has been documented during maternal withdrawal from opiates.[20] Pregnant women who are dependent on opiates and their fetuses do better on a regimen of methadone rather than being untreated.[21] The advantages of methadone maintenance treatment during pregnancy include longer gestational periods and higher birth weights than in mothers who are heroin users and are not treated,[22] as well as a lower risk of fetal exposure to infectious diseases contracted through needle sharing.[5]

Lower concentrations of methadone in the plasma and increased methadone clearances have been reported during pregnancy, likely due to increased metabolism.[23] Higher doses may be required, especially in the third trimester. Dosage should be tailored to the individual during pregnancy to minimize the chance to relapse to heroin use and prevent withdrawal symptoms.

Neonates born to women who are dependent on methadone are at risk of developing an opiate abstinence syndrome, but the syndrome tends to develop more slowly, is more moderate in severity, and lasts longer than in infants born to heroin-dependent women.[24]

DRUG INTERACTIONS

The interaction of other drugs with methadone may be classified as either pharmacodynamic (having effects on the mechanism of action) or pharmacokinetic (having effects on absorption, distribution, and elimination).[25] These interactions may vary in their magnitude and do not necessarily prohibit the concomitant administration of other drugs. The table provides examples of drug interactions with methadone.[25-30]

OVERDOSE AND ADVERSE REACTIONS

Although methadone's long duration of action may be advantageous from a therapeutic perspective, it is a risk factor for overdose.[32] Because of accumulation of the drug, it may be difficult to increase the dose in patients who are not tolerant to methadone. In addition, methadone has a prolonged interval of toxicity that may extend to several hours or days, and it is, therefore, important to observe patients for about 48 hours after a methadone overdose. Another important risk factor includes extremes of age (infants and elderly patients) because of differences in the pharmacokinetics and pharmacodynamics of methadone in these patients. For example, one 10-mg tablet (a therapeutic adult dose) has killed a child,[33] and 30 mg administered intravenously caused respiratory depression for several days in an 81 year old.[34] The most severe consequential effect from methadone is the potential for apnea, respiratory failure, and hypoxia, leading to coma, seizures, hypotension, and death. This effect may account for the deaths in patients that occurred when methadone was initiated at high doses in methadone maintenance programs.[35] Other deaths may be attributed to the use of multiple drugs and substances (for example, alcohol) with methadone. Naloxone, an opiate antagonist, can reverse methadone's toxic effects in patients with overdose. Noncardiogenic pulmonary edema has resulted from therapeutic doses.[36] Other adverse effects associated with long-term administration have included increased sweating, constipation, appetite disturbances, sexual dys-

Table *Drug interactions with methadone*

Drug	Interaction type	Clinical effect	Practitioner considerations
Naloxone, naltrexone, pentazocine, nalbuphine-mixed opiate antagonists/partial agonists	Pharmacodynamic—receptor blockade	Precipitate abstinence syndrome	Must avoid in patients on methadone therapy; may use naloxone to treat overdose
Rifampin, carbamazepine, phenytoin,[26] nevirapine[27]	Pharmacokinetic—enhance elimination	Reduce blood concentrations and effectiveness and may produce abstinence syndrome	Increase dose of methadone
Benzodiazepines, ethanol	Pharmacodynamic—additive/synergistic CNS depression	Increased sedation and risk of respiratory failure	Avoid in patients on methadone therapy
Ritonavir,[28] fluvoxamine[29]	Pharmacokinetic—decreased metabolism	Produce methadone toxicity	Reduce dose of methadone
Zidovudine,[30] desipramine[31]	Pharmacokinetic—reduced clearance	Increased risk of zidovudine and desipramine toxicity	Reduce zidovudine dosage and monitor for toxicity; monitor desipramine serum concentrations
Thyroxine	Laboratory increased concentrations of thyroxine binding globulin	Altered thyroid function tests (increased T_3, T_4, FTI, and TBG).	Monitor for euthyroid state with free T_3 and T_4 and TSH levels
Opiate analgesics	Pharmacodynamic cross-tolerance between opioid agents	Partial tolerance to analgesic effect of opioids	Titrate and adjust dosage interval to attain analgesia, avoid mixed agonist-antagonists (eg. pentazocine) or substitute with non-narcotic analgesics (eg. NSAIDs)

T_3 = triiodothyronine, T_4 = thyroxine, FTI = free thyroxine index, TBG = thyroxine binding globin; TSH = thyroid-stimulating hormone; NSAIDs = nonsteroidal anti-inflammatory drugs

function, abnormal menses, urinary retention, rash, blurred vision, sedation, irritability, insomnia, biliary pain, hypoventilation, generalized edema, gynecomastia, galactorrhea in men and women, hepatotoxicity, and gastrointestinal symptoms.[37,38] Although these effects are usually transient and not life-threatening, they may foster nonadherence or intolerance to the long-term use of methadone.

CONCLUSIONS

Methadone is a long-acting opiate used in the treatment of opiate dependence and detoxification and for patients having chronic, severe pain. There is increasing evidence that long-term methadone use in patients who are dependent on opiates has substantial societal benefits, including diminishing illicit opiate use, reducing the transmission of HIV and hepatitis, and decreasing criminal activity and healthcare costs in this population.[39] A number of obstacles to methadone treatment exist. These include restrictive governmental regulations, the stigma of opiate addiction, and the lack of healthcare practitioners and clinics sanctioned by Food and Drug Administration that are capable of providing therapy to all patients who may benefit.

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